Bull Soc Chim Fr (1997) 134, 517-523

A convenient access to *N,N*-disubstituted amides derived from (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid

Céline Pérollier, Jacques Pécaut, René Ramasseul, Jean-Claude Marchon*

*Laboratoire de Chimie de Coordination**, Service de Chimie Inorganique et Biologique, Département de Recherche Fondamentale sur la Matière Condensée, CEA-Grenoble, 38054 Grenoble, France*

(Received 27 December 1996; accepted 4 April 1997)

Summary — Enantiopure *N,N*-disubstituted amides are obtained in good yield from (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid in three steps: dithiane protection of the aldehyde function; amidation of the carboxylic acid function; dethioketalization. Mono-*N*-substituted amides rearrange to a bicyclic lactam form. The X-ray structure of a dithiane-protected mono-*N*-substituted amide intermediate is reported.

chrysanthemic acid / biocartol / chiroporphyrin / stereochemistry

Résumé — Une voie d'accès pratique aux amides *N,N*-disubstitués dérivés de l'acide (1*R*,3*S*)-(−)-2,2-diméthyl-3-formylcyclopropane-1-carboxylique. À partir de l'acide (1*R*,3*S*)-(−)-2,2-diméthyl-3-formylcyclopropane-1-carboxylique on obtient avec un bon rendement des amides *N,N*-disubstitués énantiopurs en trois étapes : protection de la fonction aldéhyde par un dithiane ; formation de l'amide ; déprotection. Les amides *N*-monosubstitués se réarrangent en une forme lactame bicyclique. La structure aux rayons X d'un intermédiaire dithiane-amide mono-*N*-substitué est décrite.

acide chrysanthémique / biocartol / chiroporphyrine / stéréochimie

Introduction

Esters of (1*R*,3*S*)-chrysanthemic acid derivatives, such as deltamethrin, are among the most potent synthetic insecticides [1]. The related esters of (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid [2] (also called (1*R*, *cis*)-caronaldehyde or biocartol) have been described in the literature [3]. Recently, the methyl ester has also been used in the synthesis of 'chiroporphyrins', a family of macrocyclic asymmetric catalysts with stereocenters near the plane of the porphyrin ring [4]. For obtaining improved asymmetric induction by chiroporphyrins with increased steric bulk near the metal center, we have explored the synthetic chemistry of biocartol amides, a class of compounds which to our knowledge has not been investigated in detail [5]. In this paper, we report a convenient synthesis of *N,N*-disubstituted amides derived from biocartol [6], and we show that the monosubstituted *N*-benzylic and *N*-phenylic amides exhibit a preference for a bicyclic lactam form. The dithiane-protected monosubstituted *N*-benzylic amide is stable in the open form, and we describe its X-ray structure.

Results and discussion

Access to biocartol amides

Previous studies in this laboratory [4b] have shown that thioketalization of the aldehyde function of biocartol **1** with propane-1,3-dithiol takes place without epimerization at C-3. The resulting dithianecarboxylic acid **2** has become a cornerstone in the synthesis of biocartol esters [7]. Herein we show that it is also a convenient starting material for the synthesis of amides, as shown in figure 1, using the *N,N'*-dicyclohexylcarbo-

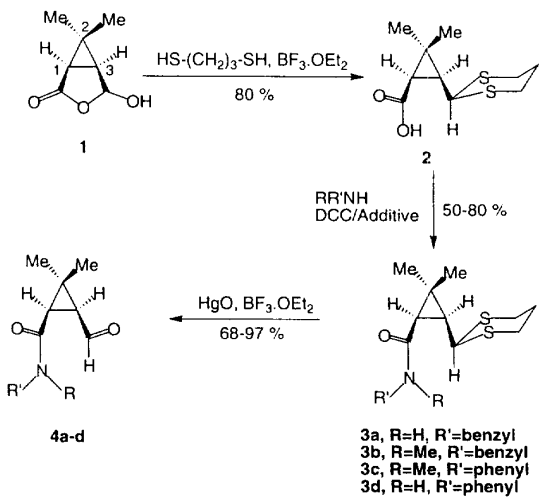

Fig 1. Three-step synthesis of *N,N*-disubstituted amides derived from biocartol.

* Correspondence and reprints. E-mail: jcmarchon@cea.fr

** Unité de Recherche Associée au CNRS 1194

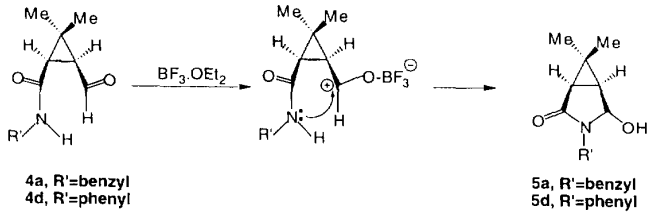

Fig 2. Proposed mechanism for the cyclisation of mono-*N*-substituted biocartol amides.

diimide/1-hydroxybenzotriazole or *N*,*N*′-dicyclohexylcarbodiimide/4-(dimethylamino)pyridine mixtures (DCC/HOBT or DCC/DMAP) as coupling reagents [8, 9].

Biocartol **1** was thioketalized at room temperature following the procedure of Vedejs [10] in 80% yield [7]. The resulting dithianecarboxylic acid intermediate **2** was reacted with benzylamine in the presence of DCC/HOBT at room temperature over 2 h, affording an 80% yield of the dithiane-protected *N*-substituted amide **3a**. A crystal of X-ray diffraction quality was selected for the structure determination of **3a** (see below).

Deprotection of **3a** by $HgO/BF_3{\cdot}Et_2O$ [10] did not give the expected aldehyde **4a**. The ^1H NMR spectrum of the product is entirely consistent with a cyclic hemiaminal form **5a** (fig 2) similar to the hemiacetal form of biocartol. Particularly noteworthy is the absence of resonances for aldehyde and N–H protons. We assume that the acidic medium required for deprotection activates the aldehyde function resulting in carbocation formation and subsequent intramolecular nucleophilic attack by the amide nitrogen atom (fig 2).

This cyclization pathway should be inhibited in *N*,*N*-disubstituted amides, and therefore **2** was reacted with *N*-benzylmethylamine and *N*-methylaniline. Thus (1*R*,3*S*)-(−)-*N*-benzyl-*N*-2,2-trimethyl-3-(1,3-dithia-2-yl)cyclopropane-1-carboxamide **3b** (yield with DCC/HOBT: 70%) and (1*R*,3*S*)-(−)-*N*-phenyl-*N*-2,2-trimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3c** (yield with DCC/HOBT: 37%; yield with DCC/DMAP: 65%), respectively, were obtained. Subsequent deprotection gave the expected *N*,*N*-disubstituted amides **4b–c**. A notable feature of the ^1H NMR spectra of **4b–c** (which has been found also in various related biocartol esters [7]) deserves mentioning. The values of the coupling constants between the vicinal cyclopropyl protons and between the aldehydic proton and the proton in α position (J = 8.9 and 6.2 Hz in $CDCl_3$, respectively) indicate a *cis* stereochemistry of the cyclopropanic protons and a retention of the configuration at C-3. The latter coupling constant appears as a convenient indicator of stereochemistry in this series (reported values [11] $J_{trans} \approx 3$ Hz, $J_{cis} \approx 6$ Hz).

Restricted rotation around the C(O)–N bond is observed in the ^1H NMR spectrum of **4b**. In d^6-benzene solution the aldehyde proton of **4b** gave two doublets (δ = 10.09 and 10.16 ppm at 25 °C, J = 5.9 Hz) in the intensity ratio 0.5:1. This is not observed for **4c**, indicating a lower rotation barrier. Due to the possible resonance structure, the C(O)–N bond of **4c** has lower bond order.

In the view of synthesizing a *N*-monosubstituted amide, we also tried to synthesize **3d** from **2** and aniline. We hoped that the reduced nucleophilicity of the amide nitrogen atom, due to the delocalized electron pair, would prevent an attack on the aldehyde function during the deprotection step. Contrary to our expectation, the cyclic product **5d** was obtained (fig 2).

X-ray structure of (1R,3S)-N-benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3a**

The unit cell includes six molecules, of which three are independent and the other three related to the former by the 2_1 symmetry axis. Figure 3 (top) shows a view of one independent molecule with the numbering scheme. Atomic coordinates and relevant crystallographic data are listed in table I. The structure solution confirms the *S*-absolute configuration of C5, C22 and C39, and the *R*-absolute configuration of C9, C26 and C43, as indicated by the low value (0.00(8)) of the Flack parameter [12] obtained after the last refinement cycle. All three independent molecules have a similar conformation with the dithiane cycle in chair form as depicted in figure 3a. The angles between the mean planes of the dithiane cycle and the phenyl ring are 129.5°, 116.3° and 124.7° respectively for each independent molecule. In each independent molecule, the carbonyl oxygen atom accepts three intramolecular C–H···O hydrogen bonds (see table III): one from the methine group located between the two sulfur atoms, one from a methyl group, and one from the benzylic methylene group. There is also an intermolecular hydrogen bond between the carbonyl oxygen atom and an amide N–H group. The donor–hydrogen–acceptor angles are much more acute than

Table I. Crystallographic data for (1*R*,3*S*)-(−)-*N*-benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3a**.

Formula	$C_{17}H_{23}NOS_2$
a, Å	10.1127(6)
b, Å	21.346(1)
c, Å	12.9667(7)
β, °	103.292(1)
V, Å^3	2724.0(3)
Space group	$P2_1$
Z	6
D_c, g/cm^3	1.176
μ, mm^{-1}	0.292
Radiation, Å	0.71073
Temperature, K	173(1)
R_1	0.0411
wR_2	0.0967

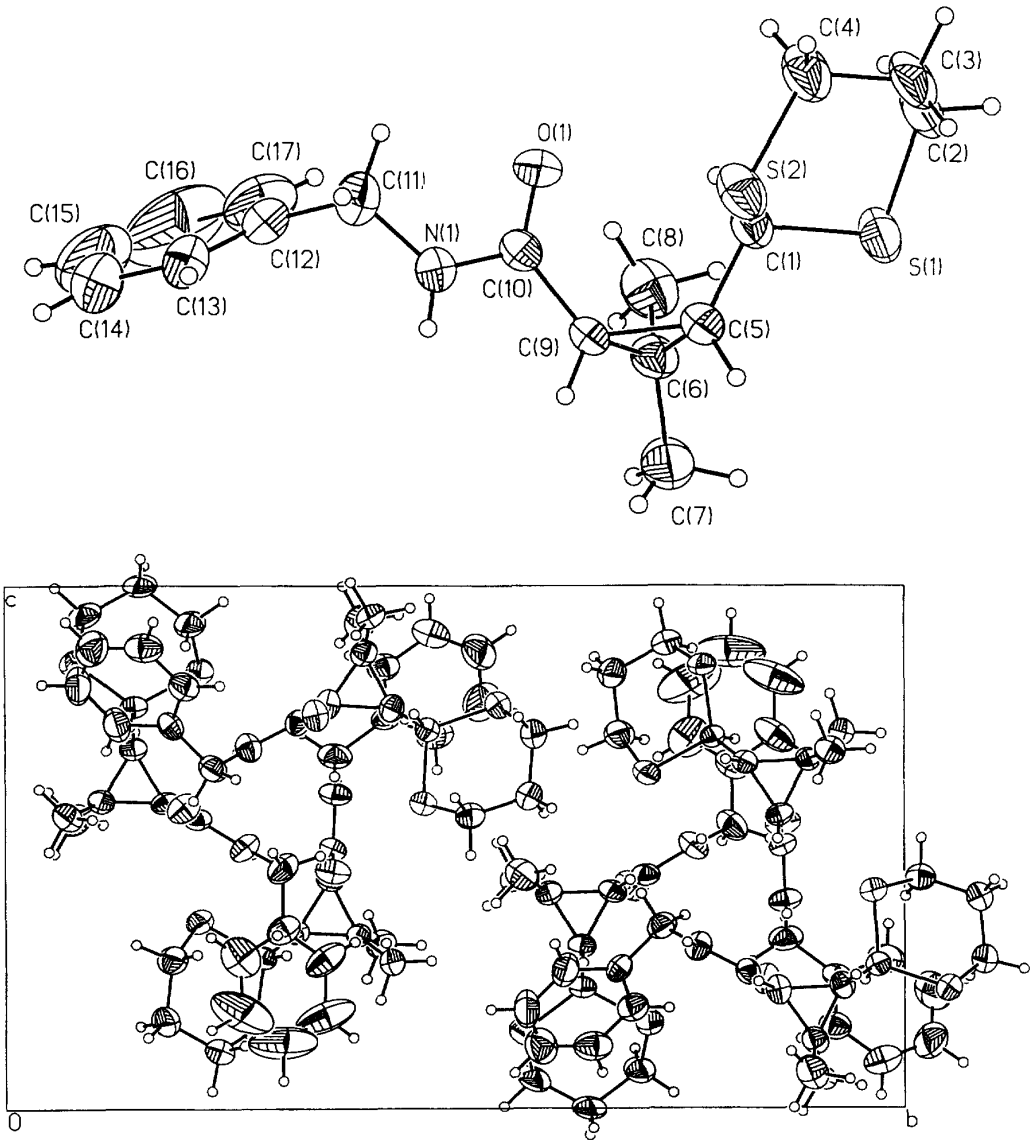

Fig 3. (Top) ORTEP view of one independent molecule of (1*R*,3*S*)-(−)-*N*-benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3a**; (bottom) projection of the packing onto the (*b*,*c*)-plane (thermal ellipsoids are drawn at the 50% probability level).

usual because of the number of donors for each acceptor. The carbonyl oxygen atom is thereby basic enough to force the molecule into a folded conformation through an extended network of short hydrogen bonds.

The three independent molecules form a helicoidal chain along the *a*-axis so that the dithiane cycle and the phenyl ring are alternated and almost parallel along this direction (fig 3 (bottom)). The angles between the mean plane of these cycles are 9.6°, 15.1° and 8.3° respectively for each independent molecule. Chain cohesion is maintained by intermolecular N–H···O hydrogen bonds. Each chain is linked to its equivalent by the two-fold axis through a rather long hydrogen bond (H(37B)–S4 = 2.842(7) Å) which connects two dithiane cycles along the *b*–*c* direction. As a consequence of this extended hydrogen bond network, the lattice can be described as a succession of (*a*,*b*) molecular planes separated by 3.68 Å between C33 and C38 along the *c*-axis. This can explain the needle shape of the crystal which has an edge that is much larger than the other two.

Experimental section

General methods

Elemental analyses were performed by CNRS-Vernaison. Infrared spectra were measured on a Perkin-Elmer 1600 Series FTIR instrument. UV-visible spectra were performed

on a Perkin-Elmer Lambda 9 instrument. Nuclear magnetic resonance spectra were obtained with a Bruker AC 200 instrument. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz in $CDCl_3$ unless otherwise noted. Spectra listed below are tabulated in the following order: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet), shoulder (sh), peak width at half-height ($w_{1/2}$, Hz), coupling constant (J, Hz), number of protons, assignment. Mass spectra were determined on a ZAB2-SEQ instrument. All solvents were used without purification except THF and CH_2Cl_2 which were dried over alumina. Thin-layer chromatography was performed by using Merck precoated silica plates 60F-254. The plates were visualized with UV light. Silica gel of the size 230–400 mesh was used for column chromatography.

X-ray structure determination

Crystals of X-ray quality were grown from a methanol solution. A white crystal of parallelepiped shape and with dimensions 0.5 × 0.08 × 0.08 mm was selected from the crystallization solution and it was employed for X-ray structure determination on a Siemens three-circle diffractometer with a CCD detector. The cell parameters were obtained with intensities detected on three batches of 15 frames with a 10 s exposure time for each. The crystal–detector distance was 6 cm. Data collection was performed at room temperature, and each one of the 1200 frames was collected for 30 s because of the small crystal size. A total of 4829 unique intensities with $-10 < h < 10$, $-21 < k < 20$, $-12 < \ell < 9$ and $1.6 < \theta < 20°$ collected on all frames using the SAINT program [13] were used to refine the values of the cell parameters: $a = 10.1127(6)$ Å, $b = 21.346(1)$ Å, $c = 12.9666(7)$ Å, $\beta = 103.292(1)°$, $Z = 6$. Intensities corrected for Lorentz and polarization factors were also corrected for absorption with the SADABS program. Space group $P2_1$ was determined from systematic absence studies, and it was confirmed by the successful structure solution (see table I). Complete information on crystal data and data collection parameters is given in the supplementary material available.

The structure was solved by direct methods using SHELXTL [14], and all non-hydrogen atoms were found with difference Fourier syntheses. Hydrogen atoms were fixed on carbon atoms using the sp^3 or sp^2 hybridization geometries. All non-hydrogen atoms were anisotropically refined on F^2. Table II and table III list respectively the atomic coordinates and the hydrogen bond distances and angles. Hydrogen atom coordinates, interatomic distances and angles, and isotropic displacement parameters are listed in the supplementary material available. Final R indices on 4670 data with $F_0 > 4\sigma(F_0)$ and 569 parameters are $R_1 = 0.041$ and $wR_2 = 0.0967$. The $1/\sigma^2$ weighting scheme was used for final refinement. The largest electronic density residual peak and hole are 0.124 and $-0.117e^-/Å^3$ respectively.

Synthetic procedures

- *(1R,3S)-2,2-Dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxylic acid* **2**

This compound was prepared according to a procedure worked out earlier in this laboratory for the synthesis of biocartol esters [7].

- *(1R,3S)-(−)-N-Benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide* **3a**

HOBT (3.83 g, 25 mmol), **2** (5.8 g, 25 mmol), benzylamine (2.76 mL, 25 mmol) were dissolved in 50 mL of THF. To the mixture, DCC (5.42 g, 26.25 mmol) was added with stirring

Table II. Atomic coordinates (Å) and equivalent isotropic displacement parameters (Å^2) for (1*R*,3*S*)-(−)-*N*-benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3a**.

	x	y	z	U(eq)
S(1)	0.3378(2)	0.5763(1)	0.1448(1)	0.088(1)
S(2)	0.3263(2)	0.7172(1)	0.1624(1)	0.086(1)
S(3)	0.9344(2)	0.4657(1)	0.5831(1)	0.077(1)
S(4)	0.9525(2)	0.5496(1)	0.7718(1)	0.085(1)
S(5)	0.2126(2)	0.2150(1)	0.3585(1)	0.077(1)
S(6)	0.0887(2)	0.2760(1)	0.1513(1)	0.085(1)
O(1)	0.2674(4)	0.6977(2)	0.4251(3)	0.084(1)
O(2)	1.1123(5)	0.3461(2)	0.7530(3)	0.173(1)
O(3)	0.3553(4)	0.3651(2)	0.4542(3)	0.080(1)
N(1)	0.4292(5)	0.7660(2)	0.5010(4)	0.176(1)
N(2)	0.9606(5)	0.2709(2)	0.6911(4)	0.174(1)
N(3)	0.2780(4)	0.3677(2)	0.6025(4)	0.074(1)
C(1)	0.3417(6)	0.6426(2)	0.2314(4)	0.066(2)
C(2)	0.1734(7)	0.5885(3)	0.0561(5)	0.099(2)
C(3)	0.1574(7)	0.6500(4)	0.0004(5)	0.102(2)
C(4)	0.1625(7)	0.7059(3)	0.0726(5)	0.104(2)
C(5)	0.4743(5)	0.6419(3)	0.3109(4)	0.064(2)
C(6)	0.5008(6)	0.6059(3)	0.4117(4)	0.066(2)
C(7)	0.6380(7)	0.5761(3)	0.4465(6)	0.114(3)
C(8)	0.3885(7)	0.5685(3)	0.4413(5)	0.099(2)
C(9)	0.4964(6)	0.6767(3)	0.4151(4)	0.061(2)
C(10)	0.3871(7)	0.7133(3)	0.4459(4)	0.063(2)
C(11)	0.3417(7)	0.8089(3)	0.5402(5)	0.097(2)
C(12)	0.3654(7)	0.8091(4)	0.6573(6)	0.088(2)
C(13)	0.4355(8)	0.8561(5)	0.7145(8)	0.122(3)
C(14)	0.456(1)	0.8556(9)	0.824(1)	0.200(8)
C(15)	0.402(2)	0.808(2)	0.874(1)	0.25(2)
C(16)	0.342(2)	0.762(1)	0.815(2)	0.25(1)
C(17)	0.3189(9)	0.7606(5)	0.7095(1)	0.138(3)
C(18)	0.9700(6)	0.4706(3)	0.7252(4)	0.068(2)
C(19)	1.0643(7)	0.5181(3)	0.5596(5)	0.083(2)
C(20)	1.0552(7)	0.5837(3)	0.5970(5)	0.084(2)
C(21)	1.0775(7)	0.5892(3)	0.7164(5)	0.090(2)
C(22)	0.8725(6)	0.4307(3)	0.7659(4)	0.066(2)
C(23)	0.9075(6)	0.4005(3)	0.8720(5)	0.070(2)
C(24)	0.7938(8)	0.3972(3)	0.9327(6)	0.107(2)
C(25)	1.0460(7)	0.4082(3)	0.9422(5)	0.089(2)
C(26)	0.8856(6)	0.3600(3)	0.7737(4)	0.066(2)
C(27)	0.9963(7)	0.3260(3)	0.7391(4)	0.062(2)
C(28)	1.0548(7)	0.2306(3)	0.6518(5)	0.080(2)
C(29)	1.1236(6)	0.1835(3)	0.7327(5)	0.067(2)
C(30)	1.0721(8)	0.1235(4)	0.7355(6)	0.104(2)
C(31)	1.134(1)	0.0807(4)	0.8103(9)	0.126(3)
C(32)	1.248(1)	0.0966(5)	0.8818(8)	0.122(3)
C(33)	1.3016(8)	0.1544(6)	0.8817(6)	0.108(2)
C(34)	1.2390(7)	0.1985(3)	0.8076(6)	0.086(2)
C(35)	0.1692(6)	0.2874(2)	0.2886(4)	0.059(2)
C(36)	0.3276(7)	0.1845(3)	0.2848(5)	0.092(2)
C(37)	0.2690(8)	0.1769(3)	0.1672(5)	0.094(2)
C(38)	0.2246(7)	0.2371(3)	0.1098(5)	0.091(2)
C(39)	0.0725(6)	0.3236(3)	0.3377(4)	0.058(2)
C(40)	0.0580(6)	0.3930(3)	0.3324(4)	0.060(2)
C(41)	−0.0859(6)	0.4178(3)	0.3148(5)	0.083(2)
C(42)	0.1507(7)	0.4304(3)	0.2800(5)	0.082(2)
C(43)	0.1153(5)	0.3615(2)	0.4383(4)	0.059(1)
C(44)	0.2587(6)	0.3652(3)	0.4973(4)	0.060(2)
C(45)	0.4098(7)	0.3678(3)	0.6756(5)	0.094(2)
C(46)	0.4275(6)	0.4248(3)	0.7473(5)	0.067(2)
C(47)	0.4690(8)	0.4792(5)	0.7149(6)	0.117(3)
C(48)	0.485(1)	0.5316(6)	0.778(1)	0.155(4)
C(49)	0.454(1)	0.5290(5)	0.874(1)	0.140(4)
C(50)	0.4115(8)	0.4754(6)	0.9094(6)	0.112(3)
C(51)	0.3977(6)	0.4222(4)	0.8444(6)	0.085(2)

Table III. Selected bond lengths (Å) and angles (°) for (1*R*,3*S*)-(−)-*N*-benzyl-2,2-dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide **3a**.

Intramolecular hydrogen bonds	
C(1)–H(1)	0.98
H(1)---O(1)	2.393(9)
C(1)–H(1)---O(1)	121.4(3)
C(8)–H(8A)	0.96
H(8A)---O(1)	2.229(9)
C(8)–H(8A)---O(1)	137.3(3)
C(11)–H(11A)	0.97
H(11A)---O(1)	2.43(1)
C(11)–H(11A)---O(1)	103.0(4)
C(18)–H(18)	0.98
H(18)---O(2)	2.40(1)
C(18)–H(18)---O(2)	119.7(5)
C(25)–H(25C)	0.96
H(25C)---O(2)	2.224(9)
C(25)–H(25C)---O(2)	136.7(4)
C(28)–H(28A)	0.97
H(28A)---O(2)	2.50(1)
C(28)–H(28A)---O(2)	97.0(4)
C(35)–H(35)	0.98
H(35)---O(3)	2.387(8)
C(35)–H(35)---O(3)	120.6(4)
C(42)–H(42C)	0.96
H(42C)---O(3)	2.255(9)
C(42)–H(42C)---O(3)	137.0(5)
C(45)–H(45A)	0.97
H(45A)---O(3)	2.405(9)
C(45)–H(45A)---O(3)	103.6(3)
N(1)–H(1N)	0.86
H(1N)---O(3)	2.319(8)
N(1)–H(1N)---O(3)	135.8(5)
N(2)–H(2N)	0.86
H(2N)---O(1)	2.207(8)
N(2)–H(2N)---O(1)	138.0(2)
N(3)–H(3N)	0.86
H(3N)---O(2)	2.117(8)
N(3)–H(3N)---O(2)	148.7(3)
C(37)–H(37B)	0.97
H(37B)---S4	2.842(7)
C(37)–H(37B)---S4	150.8(2)

at 0 °C. The mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature over 1 h. After filtering the solution, the solvent was removed in vacuo. The organic residue was dissolved in EtOAc (60 mL) and extracted with saturated aqueous $NaHCO_3$ solution (3 × 25 mL), with 0.2 N HCl (3 × 25 mL) and water (3 × 25 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The solid was recrystallized from methanol. Workup gave 6.4 g (80 %) of compound **3a** as a white solid.

F 146 °C. $[\alpha]_D^{28} = -64$, $c = 2.1$, ethanol.

IR (nujol) ν_{max} 3 291 (N–H), 1 642 (C(O)–N) cm^{-1}.

UV (ethanol) λ_{max} (log ε) = 250.5 (2.95) nm.

^1H NMR δ 1.15 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.22 (dd, J_1 = 8.5 Hz, J_2 = 11.0 Hz, 1H, CH–C*H*–CH), 1.36 (d, J_1 = 8.6 Hz, 1H, C*H*–C(O)N), 1.79 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.06 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.80 (m, 4H, CH_2–S), 4.35 (dd, J_3 = 5.4 Hz, J_4 = 14.8 Hz, 1H, N–CH), 4.50 (dd, J_3 = 5.9 Hz, J_4 = 14.8 Hz, 1H, N–CH), 4.54 (d, J_2 = 11.3 Hz, 1H, CH–S), 6.10 (m, $w_{1/2}$ = 16.5 Hz, 1H, N–H), 7.2–7.32 (m, 5H, C_6H_5).

Anal calc for $C_{17}H_{23}NOS_2$: C, 63.55; H, 7.17; N, 4.36; S, 19.94. Found: C, 63.71; H, 7.11; N, 4.19; S, 20.18.

MS (FAB$^+$) 322.2 (MH^+).

• *(1R,3S)-(−)-3-Benzyl-4-hydroxy-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-one* **5a**

A mixture of red HgO (7.9 g, 36.5 mmol; 2 equiv) and BF_3·OEt_2 (4.5 mL, 36.6 mmol, 2 equiv) in 30 mL of THF and 10 mL of distilled water was stirred over 30 min. A solution of amide **3a** (4.2 g, 18.2 mmol, 1 equiv) in THF (15 mL) was added dropwise with stirring. After stirring for 30 min at room temperature, 150 mL of diethyl ether was added under vigorous stirring over 10 min. The precipitate was collected by filtration and the organic layer was successively washed with a saturated aqueous $NaHCO_3$ solution and brine, and dried. The solvent was then removed in vacuo. The bicyclic compound **5a** was obtained as a white solid in 94% yield.

F 123 °C. $[\alpha]_D^{28} = -115$, $c = 1.79$, ethanol.

IR (nujol) ν_{max} 3 273 (OH), 1 650 (C(O)–N) cm^{-1}.

^1H NMR δ 0.72 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.66 (d, J_1 = 5.9 Hz, 1H, C*H*–C(O)N), 1.87 (dd, J_1 = 5.9 Hz, J_2 = 1.6 Hz, 1H, C*H*–CH(OH)), 3.09 (m, 1H, OH), 4.17 (d, J_3 = 14.2 Hz, 1H, N–CH), 4.60–4.72 (m, 2H), 7.24–7.28 (m, 5H, C_6H_5).

^1H NMR ($CDCl_3$, D_2O) δ 0.73 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.65 (d, J_1 = 5.9 Hz, 1H, C*H*–C(O)N), 1.88 (dd, J_1 = 5.9 Hz, J_2 = 1.9 Hz, 1H, C*H*–CH(OD)), 4.18 (d, J_3 = 14.2, 1H, N–CH), 4.63–4.78 (m, 2H), 7.24–7.29 (m, 5H, C_6H_5).

^1H NMR (C_6D_6) δ 0.53 (s, 3H, CH_3), 0.59 (s, 3H, CH_3), 1.24 (d, J_1 = 6.2 Hz, $w_{1/2}$ = 5.6 Hz, 1H, C*H*–CH(OH)), 1.71 (d, J_1 = 6.2 Hz, 1H, C*H*–C(O)N), 2.60–2.90 (broad d, $J \approx 12$ Hz, $w_{1/2}$ = 53 Hz, 1H, CH(O*H*)), 4.08 (d, J_3 = 14.2 Hz, 1H, N–CH), 4.44 (d, J_4 = 11.0 Hz, $w_{1/2}$ = 5.6 Hz, 1H, C*H*–OH), 4.81 (d, J_3 = 14.2 Hz, 1H, N–CH), 6.96–7.36 (m, 5H, C_6H_5).

^1H NMR (C_6D_6, D_2O) δ 0.53 (s, 3H, CH_3), 0.59 (s, 3H, CH_3), 1.22 (m, 1H), 1.71 (m, 1H), 4.08 (d, J_1 = 13.7 Hz, 1H, N–CH), 4.42 (s, $w_{1/2}$ = 7.1 Hz, 1H, C*H*–OD), 4.79 (d, J_1 = 13.7 Hz, 1H, N–CH), 6.70–7.36 (m, 5H, C_6H_5).

MS (FAB$^+$) 232.2 (MH^+).

• *(1R,3S)-N-Benzyl-N-2,2-trimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide* **3b**

Using a procedure similar to that described for **3a**, compound **2** (12.7 g, 54.7 mmol) was reacted with *N*-benzylmethylamine (8.7 mL, 65.7 mmol, 1.2 equiv), HOBT (9.1 g, 1.16 equiv) and DCC (17.1 g, 1.5 equiv). The resulting yellow oil was purified by silica gel chromatography, eluting with petroleum ether/diethyl ether (50:50) to afford 12.8 g (70%) of colorless oil.

IR (nujol) ν_{max} 1 645 (C(O)–N) cm^{-1}.

^1H NMR δ 0.99 and 1.18 (2s, 3H, CH_3), 1.27 and 1.32 (2s, 3H, CH_3), cyclopropanic protons in β position of the dithiane overlap with the previous peaks, 1.59 and 1.68 (2d, J_1 = 8.6 Hz, 1H, C*H*–C(O)N), 1.79 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.06 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.83 (m, 4H, 2 × CH_2–S), 2.93 (s, 3H, N–Me), 4.61 and 4.75 (2d, J_2 = 11.3 Hz, 1H, CH–S), 4.66 (d, J_3 = 16.1 Hz, 1H, N–CH), 4.46 and 4.53 (2d, J_3 = 16.1 Hz, 1H, N–CH), 7.22 (m, 5H, C_6H_5).

Anal calc for $C_{18}H_{25}NOS_2$: C, 64.5; H, 7.5; N, 4.2; S, 19.1. Found: C, 65.0; H, 7.7; N, 4.0; S, 19.5.

MS (FAB$^+$) 336.3 (MH^+).

• *(1R,3S)-(−)-N-Benzyl-3-formyl-N-2,2-trimethylcyclopropane-1-carboxamide* **4b**

To a mixture of red HgO (5.3 g, 24 mmol; 1.2 equiv) and $BF_3{\cdot}OEt_2$ (3 mL, 24 mmol, 1.2 equiv) in 43 mL of THF and 7 mL of distilled water was added dropwise with stirring a solution of amide **3b** (6.7 g, 20 mmol, 1 equiv) in THF (10 mL). After stirring for 45 min at room temperature, anhydrous Na_2SO_4 was added followed by diethyl ether (150 mL) under vigorous stirring. The precipitate was collected by filtration and washed with EtOAc and the filtrate was washed with saturated aqueous Na_2CO_3 solution and dried. The solvent was removed in vacuo. An oil was obtained, 4.6 g (94%).

$[\alpha]_D^{28} = -93$, $c = 2.08$, ethanol.

IR (nujol) ν_{max} 1 701 (C(O)–H), 1644 (C(O)–N) cm^{-1}.

^1H NMR δ 1.11 and 1.28 (2s, 3H, CH_3), 1.42 and 1.44 (2s, 3H, CH_3), 1.69 and 1.76 (2dd, $J_1 = 6.2$ Hz, $J_2 = 8.9$ Hz, 1H, C*H*–C(O)H), 2.21 and 2.27 (2d, $J_2 = 8.9$ Hz, 1H, C*H*–C(O)N), 2.97 (1s, 3H, N–Me), 4.42 and 4.50 (2d, $J_3 = 14.8$ Hz, 1H, N–CH), 4.71 (1d, $J_3 = 14.8$ Hz, 1H, N–CH), 7.26 (m, 5H, C_6H_5), 9.67 and 9.70 (2d, $J_1 = 6.2$ Hz, 1H, C(O)H) or in C_6D_6 10.09 and 10.16 (2d, $J = 5.9$ Hz).

Anal calc for $C_{15}H_{19}NO_2$, 0.2 H_2O: C, 73.5; H, 7.8; N, 5.7. Found : C, 71.8; H, 7.7; N, 5.4.

MS (FAB^+) 246.2 (MH^+).

• *(1R,3S)-(−)-N-2,2-Trimethyl-N-phenyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide* **3c**

N-methylaniline (4.9 mL, 43 mmol), **2** (5 g, 22 mmol) were dissolved in CH_2Cl_2 (20 mL). DCC (4.9 g, 24 mmol) and DMAP (130 mg, 4.3 mmol) in CH_2Cl_2 (20 mL) were added over 1.5 h at 0 °C and the mixture was stirred for 2 h at room temperature. After filtering the solution, the solvent was removed in vacuo. The organic residue was dissolved in diethyl ether and was put in the refrigerator for 15 min. After filtering, the solvent was removed in vacuo and the organic residue was dissolved in EtOAc (100 mL) and extracted with a saturated aqueous $NaHCO_3$ solution (3 × 25 mL), with 0.2 N HCl (3 × 25 mL) and water (3 × 25 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The resulting oil was purified by silica gel chromatography with petroleum ether/diethyl ether (50:50) as eluent to afford 4.53 g (65%) of a white solid.

F 102 °C. $[\alpha]_D^{27} = -111$, $c = 1.66$, ethanol.

^1H NMR δ 0.90 (s, 3H, CH_3), 1.08 (dd, $J_1 = 8.3$ Hz, $J_2 = 11.3$ Hz, CH–C*H*–CH), 1.29 (d, $J_1 = 8.3$ Hz, C*H*–C(O)N), 1.35 (s, 3H, CH_3), 1.85 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.10 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.86 (m, 4H, 2 × CH_2–S), 3.25 (s, 3H, N–Me), 4.85 (d, $J_2 = 11.3$ Hz, 1H, CH–S), 7.20–7.50 (m, 5H, C_6H_5).
MS (FAB^+) 322.3 (MH^+).

• *(1R,3S)-3-Formyl-N-2,2-trimethyl-N-phenylcyclopropane-1-carboxamide* **4c**

Using a procedure similar to that described for **4b**, compound **3c** (4.53 g, 14 mmol) was reacted with HgO (3.67 g, 17 mmol), $BF_3{\cdot}OEt_2$ (2.1 mL, 17 mmol) over 40 min. After crystallisation (petroleum ether/diethyl ether), a white solid was obtained (3.16 g, 97%).

F 62 °C.

^1H NMR δ 0.90 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.58 (dd, $J_1 = 6.2$ Hz, $J_2 = 8.9$ Hz, 1H, C*H*–C(O)H), 1.83 (d, $J_2 = 8.9$ Hz, 1H, C*H*–C(O)N), 3.29 (s, 3H, N–Me), 7.16–7.48 (m, 5H, C_6H_5), 9.83 (d, $J_1 = 6.2$ Hz, 1H, C(O)H).

Anal calc for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.5; H, 7.3; N, 6.0.

• *(1R,3S)-2,2-Dimethyl-N-phenyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxamide* **3d**

Using a procedure similar to that described for **3a**, compound **2** (6 g, 25.9 mmol) was reacted with aniline (2.8 mL, 31.1 mmol), HOBT (4.2 g, 31.1 mmol) and DCC (8.03 g, 31.1 mmol at room temperature over a period of 4 h. The resulting oil was purified by silica gel chromatography, eluting with petroleum ether/diethyl ether (50:50) to afford 4.44 g (56%) of a white solid.

F 141 °C.

^1H NMR δ 1.19 (s, 3H, CH_3), 1.30 (dd, $J_1 = 8.6$ Hz, $J_2 = 11.5$ Hz, CH–C*H*–CH), 1.36 (s, 3H, CH_3), 1.53 (d, $J_1 = 8.3$ Hz, C*H*–C(O)N), 1.86 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.09 (m, 1H, CH_2–C*H*$_2$–CH_2), 2.87 (m, 4H, 2 × CH_2–S), 4.52 (d, $J_2 = 11.6$ Hz, 1H, CH–S), 7.03–7.49 (m, 5H, C_6H_5), 7.73 (sh, 1H, NH).

• *(1R,3S)-4-Hydroxy-6,6-dimethyl-3-phenyl-3-azabicyclo[3.1.0]hexan-2-one* **5d**

Using a procedure similar to that described for **4b**, compound **3d** (2.15 g, 9.9 mmol) was reacted with HgO (2.57 g, 11.9 mmol), $BF_3{\cdot}OEt_2$ (1.46 mL, 11.9 mmol) over 30 min. An oil was obtained (1.47 g) in 68% yield.

^1H NMR δ 1.04 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.91 (d, $J_1 = 5.9$ Hz, 1H, C*H*–C(O)N), 2.36 (sh, 1H, OH), 2.59 (d, $J_1 = 5.9$ Hz, 1H, C*H*–CH(OH)), 3.30 (s, $w_{1/2} = 7.1$ Hz, 1H, C*H*(OH)), 7.1–7.4 (m, 5H, C_6H_5).

Supplementary material

Crystallographic data, data collection parameters, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and structure factors have been deposited with the British Library, Document Supply Centre at Boston Spa, Wetherby, West Yorkshire, LS23 7BQ, UK, as supplementary publication No SUP 90462 and are available on request from the Document Supply Centre.

Acknowledgments

We thank Dr Jean Buendia of Roussel Uclaf for a generous gift of biocartol, Dr Dawn Toronto for helpful discussions and for her assistance in writing the manuscript, Colette Lebrun for mass spectra, Nathalie Gon for help with the synthesis of starting materials, and a referee for his helpful comments.

References and notes

1 Martel J, In: *Chirality in Industry*, Collins AN, Sheldrake GN, Crosby J, Eds, Wiley, London, 1992, ch 4
2 Bakshi D, Mahidroo VK, Soman R, Dev S, *Tetrahedron* (1989) 45, 767
3 See for example: Martel J, Tessier J, Teche A (Roussel Uclaf), Fr Pat 81 18934 (1981)
4 a) Veyrat M, Maury O, Faverjon F, Over DE, Ramasseul R, Marchon JC, Turowska-Tyrk I, Scheidt WR, *Angew Chem Int Ed Engl* (1994) 33, 220
b) Mazzanti, M, Veyrat, M, Ramasseul, R, Marchon, JC, Turowska-Tyrk, I, Shang, M, Scheidt, WR, *Inorg Chem* (1996) 35, 3733
5 a) Martin SF, Oalmann CJ, Liras S, *Tetrahedron* (1993) 49, 3521
b) Hiemstra H, Speckamp WN, In: *Comprehensive Organic Synthesis*, Trost BM, Ed, Pergamon, London, 1991, Vol 2, part 2, ch 4.5 and references therein
6 Enantiopure biocartol was a generous gift of Roussel Uclaf ($[\alpha]_D^{25} = -102$, $c = 2$, ethanol)

7 Veyrat M, Fantin L, Desmoulins S, Petitjean A, Mazzanti M, Ramasseul R, Marchon JC, Bau R, submitted for publication in *Bull Soc Chim Fr*
8 König W, Geiger R, *Chem Ber* (1970) 103, 788
9 Neises B, Steglich W, *Angew Chem Int Ed Engl* (1978) 17, 522
10 Vedejs E, Fuchs PL, *J Org Chem* (1971) 36, 366
11 a) Majewski M, Snieckus V, *J Org Chem* (1984) 49, 2682
b) Frauenrath H, Philipps T, *Liebigs Ann Chem* (1985) 1303
12 a) Flack, HD, *Acta Crystallogr Sect A* (1983) 39, 876
b) Bernardelli G, Flack HD, ibid (1985) 41, 500
13 SMART and SAINT Area-Detector Control and Integration Software (1995), Siemens Analytical X-Ray Instruments Inc, Madison, Wisconsin, USA
14 Sheldrick GM, SHELXTL-Plus, Version 5: program for the refinement of crystal structures (1994), University of Göttingen, Germany